PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Praveen SHARMA et al. Conf. No.: **5417**

Appln. No.: **09/429,003** Group Art Unit: **1655**

Filed: **October 29, 1999** Examiner: **Einsmann, J.**

For: **METHOD OF PREPARING A STANDARD DIAGNOSTIC GENE TRANSCRIPT PATTERN**

SECOND DECLARATION UNDER RULE 132

Assistant Commissioner
of Patents
P.O. Box. 1450
Arlington, Virginia 2231-1450

I, Praveen Sharma, an Indian citizen of Waldemar Thranes gate 62D, N-0173, Oslo, Norway; and

I, Anders Lönneborg, a Swedish citizen of Feltspatveien 14, N-1430, Aas, Norway,

declare as follows:

1. We are inventors on the present application. A first Declaration was filed in connection with this application on 21 November 2002. This second Declaration supplements the evidence provided in the first Declaration. We have reviewed the Office Action dated 31 January 2003 which issued on the above application, wherein the Examiner raised objections under 35 U.S.C. 112, first paragraph, that the specification does not enable performance of the invention as claimed. We understand that this issue was discussed further, by telephonic interview, by our UK and US patent attorneys with Examiner Einsmann on 3 March 2003. We are informed that the principle issues of concern in relation to the claims relating to Alzheimer's disease are (i) the statistical significance of the differential expression of genes in diseased

versus non-diseased individuals, (ii) the types of genes whose expression varies under these circumstances, and (iii) whether comparable variation in expression occurs in a variety of different diseases and thus whether a characteristic pattern for a particular disease can be obtained. We have carried out experiments to deal with all of these issues.

2. We provide details of experiments which we have conducted in our laboratory which identify, from a pool of 730 randomly selected genes, those which are differentially expressed in Alzheimer's disease and breast cancer samples, in both cases relative to samples from patients without the disease in question. We show that, respectively, 49 and 73 of these genes are differentially expressed in Alzheimer's disease and breast cancer samples and that the differential expression is statistically significant as assessed by the t-test. For those transcripts which have been sequenced, we show that the genes which are differentially expressed are concerned with house-keeping functions in the cell and are not classically considered to be stress-related genes. Finally, we show that the 49 informative probes for Alzheimer's disease are able to diagnose Alzheimer's patients with an accuracy of 87% and similarly the 73 informative probes for breast cancer are able to diagnose breast cancer patients with an accuracy of 95%. We also show that the identified probes are specific for diagnosis of the particular disease for which they are considered informative and are unable to accurately diagnose the other disease under investigation. The experiments which have been conducted are described in the following paragraphs.

3. Samples for examination were taken from 3 groups of female patients:

(i) AD = patients with Alzheimer's disease but no reported breast cancer;

(ii) BC = patients with breast cancer but not Alzheimer's disease; and

(iii) H = healthy patients with neither breast cancer nor Alzheimer's disease.

The samples which have been examined are peripheral blood samples

taken distant to the site of disease.

4. Twelve female patients diagnosed with Alzheimer's Disease at the Memory Clinic at Ullevål University Hospital were used in the trial. These patients were not reported to have breast cancer. The patients were confirmed as having Alzheimer's disease based on the following criteria:

* A standardized interview with a care-giver using IQCODE (Informant Questionnaire on Cognitive Decline in the Elderly), an ADL (Activities of Daily Living) scale and a scale measuring behaviour of the patient (Green scale).
* Neuropsychological evaluation using MMSE (Mini Mental State Examination), Clock drawing test, Trailmaking test A and B (TMT A and B), Kendrick object learning test (visual memory test), part of the Wechsler battery and Benton test.
* A psychiatric evaluation using scales for detection of depression, MADRS (Montgomery-Asberg Depression Rating Scale) for interviewing the patient and Cornell scale for interviewing the care-giver.
* A physical examination.
* Laboratory tests of blood samples to rule out other diseases.
* CT (computerized tomography) scan of the brain.
* SPECT (Single Photon Emission Computed Tomography) of the brain.

The mean age of the patients was 72.3 with an age range of 66-83. The mean MMSE score was 22.0 (the maximum score attainable being 30).

5. Ten female patients diagnosed with breast cancer at Ullevål University Hospital were used in the study. All of the patients with breast cancer had a malignant tumour of the breast. Further details of the breast cancer patients from which blood was taken is provided in Table 1 in Annex 1.

6. Sixteen age-matched female individuals without diagnosed Alzheimer's disease or breast cancer were used as the normal control group. All had been tested with MMSE and had a minimum score of 29. The mean age of the normal control group was 74.0 and the age range 66-86.

7. Whole blood was obtained from the arms of the Alzheimer's disease, breast cancer and control group patients. In all cases 10ml of whole blood was collected in tubes containing EDTA and stored immediately at -80°C until used for mRNA extraction.

8. After transfer of the blood to PAXgene tubes, total mRNA was isolated from the blood of the Alzheimer's disease and breast cancer patients and from the control group donors according to the manufacturers's instructions (PreAnalytiX, Hombrechtikon, Switzerland). The isolated mRNA was labelled during reverse transcription in the presence of α^{33}P-dATP, yielding a labelled first strand cDNA.

9. The resulting labelled cDNA of the normal, Alzheimer's and breast cancer patients' samples was hybridized, separately, to 730 random cDNA clones, picked from a cDNA library from whole blood of 550 healthy individuals without knowledge of the gene sequence of the random cDNA clones, which were immobilized on a solid support, namely a nylon membrane, by spotting using a MicroGrid II workstation (BioRobotics Ltd, Cambridge, England).

10. The amount of labelled cDNA binding to the immobilized clone probes was assessed and quantified using a PhosphoImager to determine the relative signal for each probe and used to generate a gene expression data set for each group of patients' samples. The generated data sets were then normalized to take account of differences in the probe intensities resulting from the experimental conditions. The data sets were then analysed to identify clones within the 730 random clones which were informative for two different set ups:

Set up 1 - to distinguish between Alzheimer's disease samples (AD) and samples from non-Alzheimer's patients (H + BC); and

Set up 2 - to distinguish between breast cancer samples (BC) and samples from patients without breast cancer (H + AD).

cDNA which in parallel arrays exhibited a high degree of variance were excluded.

11. The differential expression of genes and their respective p-

values was determined using a traditional hypotheses testing approach. The t-test in the pair of relevant groups (Alzheimer/non-Alzheimer or breast cancer/non-breast cancer) was conducted using the formula:

$$t = \frac{Y_1 - Y_2}{\sqrt{S_p^2\left(\frac{1}{n_1}+\frac{1}{n_2}\right)}} = \frac{Y_1 - Y_2}{\sqrt{MSE\left(\frac{1}{n_1}+\frac{1}{n_2}\right)}}$$

in which:

$Y_1 - Y_2$, is the difference between the average of expression values of gene i in the two groups;

S_p^2 (also known as Mean Square Error - MSE) is the pooled variance of the two group; and

n_1 and n_2 are the numbers of samples in the two groups, respectively.

If the difference between $Y_1 - Y_2$ is large enough, the t value would be greater than the $t_{critical}$ ($p = 0.05$) and it would be concluded that there is a significant difference between the means.

12. In the case of set up 1 (Alzheimer versus non-Alzheimer samples), 49 genes were found to be differently expressed (p value < 0.05) in the cells from blood of patients with Alzheimer's disease versus individuals without Alzheimer's disease. Table 2 in Annex 1 shows the fold increase in expression between the two groups in set up 1 (in which a value > 1 is indicative of up-regulation and a value < 1 is indicative of down-regulation of expression of that gene) and the relative p values.

13. In the case of set up 2 (breast cancer versus non-breast cancer samples), 73 genes with a p value of < 0.05 were identified. Table 3 in Annex 1 shows the fold increase in expression and the relative p values between the two groups in set up 2. In set up 1 and set up 2 only a single transcript was identified which was considered to be differently expressed in both set ups and hence informative for both conditions. The remaining 48 and 72 genes of each set up are unique and informative to only one of the two conditions under investigation.

14. To illustrate the utility of these informative probes diagnostically, the normalized data for the 12 control, 16 Alzheimer's disease samples and 10 breast cancer samples hybridized to the transcript products of the 49 or 73 genes were examined further. The normalized data which provide the relative signal for each probe for each sample were manipulated using conventional statistical techniques known in the art at 30 April 1997 (namely Unscrambler software) to generate a classification model.

15. The ability of the general model (based on the 49 or 73 differently expressed genes) to correctly diagnose samples was determined by cross-validation. In this approach, the step of generating the classification model was performed as described above, but the data of a single sample (and its replicates if these are present) are omitted from the data used in that modelling process. The accuracy of the generated model is then determined by using that model to classify the omitted sample as belonging to the disease or non-disease class. This process is repeated for each sample to obtain information on the accuracy of diagnosis.

16. Prediction plots reflecting the ability of the generated models to correctly diagnose Alzheimer's disease or breast cancer samples are shown in Annex 2. In the 4 prediction plots shown, the disease samples appear on the x axis at +1 and the non-disease samples appear at -1. The y axis represents the predicted class membership. During prediction, if the prediction is correct, disease samples should fall above zero and non-disease samples should fall below zero.

17. Figure 1 shows the prediction plot using the probes considered to be informative for Alzheimer's disease in which the model has been generated for set up 1 (ie. to identify Alzheimer disease samples). If will be seen that the non-Alzheimer samples are almost all correctly predicted as non-Alzheimer samples (ie. they fall in the lower left quadrant - below 0). On the other hand, most Alzheimer samples are correctly predicted, ie. have a value greater than 0 (upper right quadrant). It is worth noting that the test is able to identify samples from Alzheimer's disease

patients even relative to patients with a different disease, ie. breast cancer. Figure 2 similarly shows that the 73 breast cancer specific genes accurately identify most breast cancer samples positively and all non-breast cancer samples (including those with Alzheimer's disease) negatively.

18. Figures 3 and 4 show however that the informative probes are specific to the disease for which they are considered informative and can not be used for diagnosis of a different disease. Figure 3 shows a prediction plot in which the probes considered to be informative for Alzheimer's disease were used to generate a model for set up 2 (ie. to identify breast cancer samples). It will be noted from the prediction plot that these probes failed to identify a single breast cancer sample correctly (all samples instead fell in the lower right quadrant, below 0). Similarly Figure 4 shows that breast cancer probes can not successfully be used to identify Alzheimer samples. Most Alzheimer samples were considered to be negative, ie. fell in the lower right quadrant.

19. These results and analysis of the diagnostic capabilities of the identified informative probes are shown in tabular form (Tables 4 - 7) in Annex 3. It will be seen from tables 4B and 5B that the use of the correct probe set for diagnosis yielded an accuracy prediction rate of 87% for Alzheimer's disease and 95% for breast cancer.

20. Eight of the 49 Alzheimer-specific probes have been sequenced and details of their sequence information and their ascribed putative function is shown in Table 8 in Annex 4. It will be noted that the proteins which are encoded are not considered traditional stress-related proteins which are induced in response to environmental stresses (ie. heat shock proteins or molecular chaperones) and include housekeeping genes such as genes which encode ribosomal proteins. Furthermore it will be noted that the impact on expression is variable and may be up- or down-regulated in Alzheimer's disease.

21. The above described experiments illustrate that statistically

significant differences are observed in gene expression in blood cells taken from individuals with a particular disease relative to a control group. We have also shown that the genes which are differentially expressed are different in the different diseases that have been examined. This illustrates that different diseases affect the expression of genes in a distinct and distinguishable way allowing the discrimination of different diseases based on that altered expression. The genes which are differentially expressed are not those that might commonly be expected in a stressed individual and instead reflect a fingerprint of altered expression peculiar to a particular disease. The implications for accurate diagnosis of a particular disease group relative to a normal group and also relative to individuals suffering from a distinct disease has been shown. It is our opinion that we have shown the pattern of variation in expression for different diseases is unique for each disease and allows the diagnosis of different diseases by the use of a set of probes specific for the assessment of that pattern. In particular the utility of accurately diagnosing Alzheimer's disease by a simple blood test has been shown.

22. We further declare that all statements made herein of our own knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Codes, and that such wilful false statements may jeopardize the validity of the application and any patent issuing thereon.

Praveen Sharma ..... 7th August, 2003

Praveen Sharma Date

Anders Lönneborg ..... 7 August 2003

Anders Lönneborg Date

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ANNEX 1

Table 1: Details of breast cancer patients used in study

Sample number	Age	Disease Stage	Breast cancer subtype	Size histology (mm)
1	69	I	IDC	15
2	60	0	DCIS	40
3	60	0	DCIS	40
4	74	I	IDC	11
5	69	I	IDC	14
6	81	I	IDC	<10
7	70	I	IDC	10
8	80	I	IDC	17
9	65	I	IDC	15
10	58	I	IDC	15

IDC = invasive ductal carcinoma
DCIS = ductal carcinoma *in situ*
Stage 0 = *in situ* carcinoma
Stage II = invasive carcinoma with tumour size <20mm

Table 2: Genes statistically significantly expressed in Alzheimer's relative to non-Alzheimer's samples

Clone number	Clone ID	Fold change	p-value
1	II-70	2.68	0.0000
2	VI-69	2.76	0.0001
3	VI-87	2.96	0.0003
4	VII-60	2.29	0.0003
5	V-70	2.08	0.0009
6	V-32	2.27	0.0010
7	VII-72	2.10	0.0025
8	VII-52	1.87	0.0026
9	VII-08	2.58	0.0035
10	I-52	2.15	0.0067
11	VI-47	2.01	0.0086
12	II-25	1.77	0.0090
13	VIII-55	1.82	0.0094
14	III-93	1.95	0.0119
15	VII-59	1.49	0.0131
16	II-66	0.67	0.0149
17	VII-54	2.00	0.0152
18	VII-49	0.60	0.0158
19	VI-72	1.79	0.0160
20	III-86	1.94	0.0166
21	VIII-65	0.68	0.0187
22	VIII-58	0.71	0.0193
23	I-26	1.52	0.0227
24	II-42	0.79	0.0230
25	VII-62	1.34	0.0247
26	VIII-59	1.99	0.0257
27	VII-50	1.72	0.0258
28	VI-63	1.99	0.0280
29	VI-04	0.66	0.0294
30	VI-59	1.86	0.0294

31	III-92	1.92	0.0302
32	III-47	1.36	0.0304
33	III-85	0.62	0.0329
34	VIII-49	0.68	0.0330
35	IV-05	0.70	0.0339
36	II-24	1.69	0.0353
37	I-66	0.72	0.0354
38	VII-40	1.94	0.0355
39	III-72	1.74	0.0366
40	II-95	1.63	0.0371
41	VIII-43	0.80	0.0372
42	IV-76	0.71	0.0382
43	VII-74	0.65	0.0393
44	V-69	1.47	0.0397
45	VII-38	0.69	0.0414
46	I-31	0.65	0.0422
47	VIII-45	0.72	0.0490
48	III-83	0.65	0.0492
49	I-70	1.55	0.0498

Table 3: Genes statistically significantly expressed in breast cancer relative to non-breast cancer samples

Clone number	Clone ID	Fold change	p-value
1	VI-26	13.10	0.0000
2	I-53	2.93	0.0000
3	I-77	2.57	0.0000
4	I-86	2.58	0.0000
5	VII-23	4.38	0.0000
6	II-21	3.45	0.0001
7	III-53	10.41	0.0002
8	V-13	2.76	0.0002
9	II-78	2.26	0.0002
10	V-41	2.02	0.0002
11	VII-04	2.88	0.0004
12	III-23	2.22	0.0004
13	I-06	3.06	0.0004
14	VI-62	5.67	0.0006
15	I-94	1.87	0.0008
16	I-05	3.42	0.0008
17	I-39	0.47	0.0008
18	VI-03	3.43	0.0015
19	I-61	2.23	0.0017
20	II-46	1.83	0.0023
21	VI-67	1.90	0.0024
22	VI-13	2.43	0.0024
23	V-80	0.48	0.0043
24	VII-63	2.43	0.0067
25	VII-45	2.14	0.0067
26	VII-32	1.73	0.0081
27	III-60	1.80	0.0085
28	VII-39	1.93	0.0089
29	I-85	1.80	0.0095
30	IV-14	0.55	0.0115
31	V-22	2.05	0.0117

32	VII-77	0.51	0.0119
33	I-13	1.63	0.0120
34	IV-10	2.74	0.0126
35	VII-21	2.37	0.0133
36	VII-02	2.44	0.0142
37	IV-62	1.96	0.0149
38	V-27	2.12	0.0153
39	IV-38	2.08	0.0154
40	IV-51	0.55	0.0160
41	III-05	2.08	0.0163
42	III-11	2.00	0.0170
43	V-51	1.33	0.0174
44	I-19	2.77	0.0189
45	IV-44	1.98	0.0193
46	VIII-14	1.60	0.0198
47	I-93	1.52	0.0201
48	V-05	3.13	0.0203
49	VII-88	0.50	0.0231
50	III-13	2.12	0.0234
51	III-40	0.64	0.0242
52	VIII-13	1.81	0.0243
53	VII-60	0.51	0.0252
54	V-55	0.67	0.0257
55	VII-44	1.82	0.0267
56	VI-24	2.24	0.0269
57	III-45	2.04	0.0272
58	VI-16	2.04	0.0272
59	VII-61	1.80	0.0273
60	III-15	1.98	0.0273
61	VI-07	1.78	0.0275
62	VII-05	2.03	0.0288
63	III-22	1.41	0.0308
64	VI-54	0.61	0.0364
65	VI-80	0.60	0.0365

66	IV-88	0.51	0.0404
67	III-67	1.66	0.0432
68	V-31	1.42	0.0454
69	III-57	1.69	0.0467
70	I-04	1.74	0.0478
71	II-23	1.69	0.0482
72	VI-19	1.85	0.0491
73	II-22	1.87	0.0495

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ANNEX 2

Figure 1

Prediction plot to diagnose Alzheimer's disease samples (set up 1) using 49 probes considered informative for Alzheimer's disease

AD = Alzheimer's disease
BC = Breast cancer
H = healthy

Figure 1

Prediction of set up 1 using 49 genes

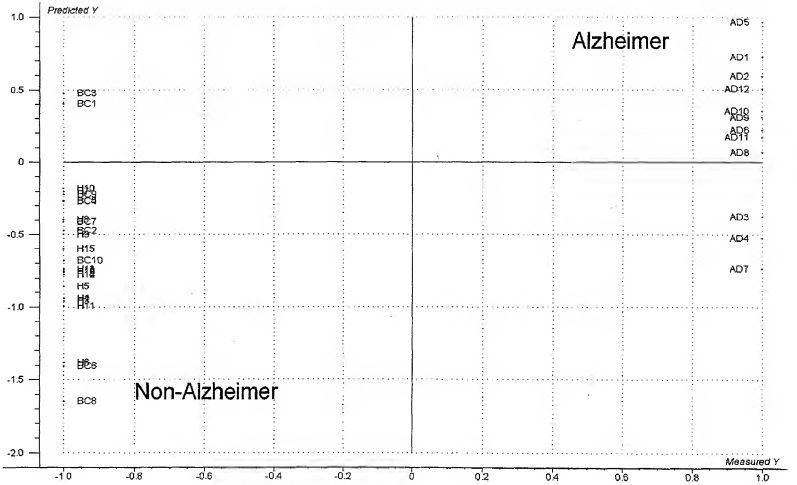


Figure 2

Prediction plot to diagnose breast cancer samples (set up 2) using 73 probes considered informative for breast cancer

AD = Alzheimer's disease
BC = Breast cancer
H = healthy

Figure 2

Prediction of set up 2 using 73 genes

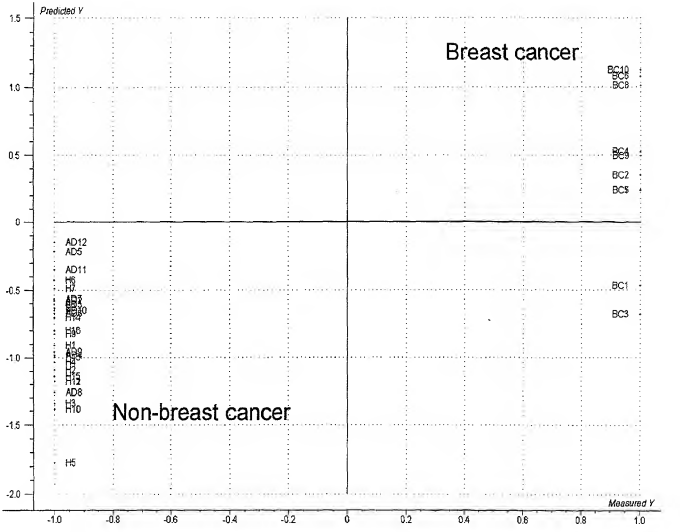


Figure 3

Prediction plot to diagnose breast cancer (set up 2) using 49 probes considered informative for Alzheimer's disease

AD = Alzheimer's disease
BC = Breast cancer
H = healthy

Figure 3

Prediction of set up 2 using 49 genes

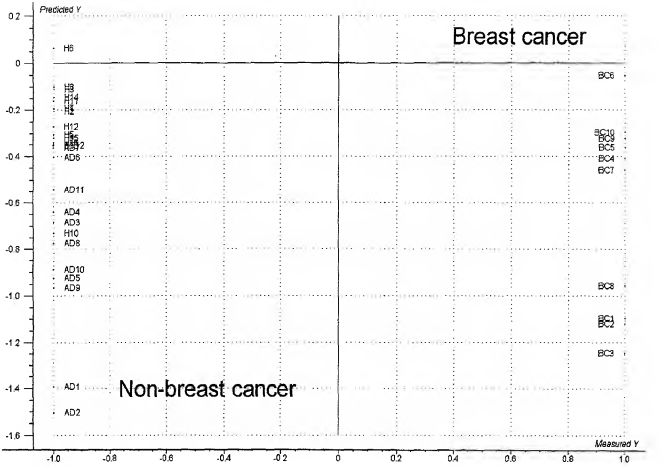


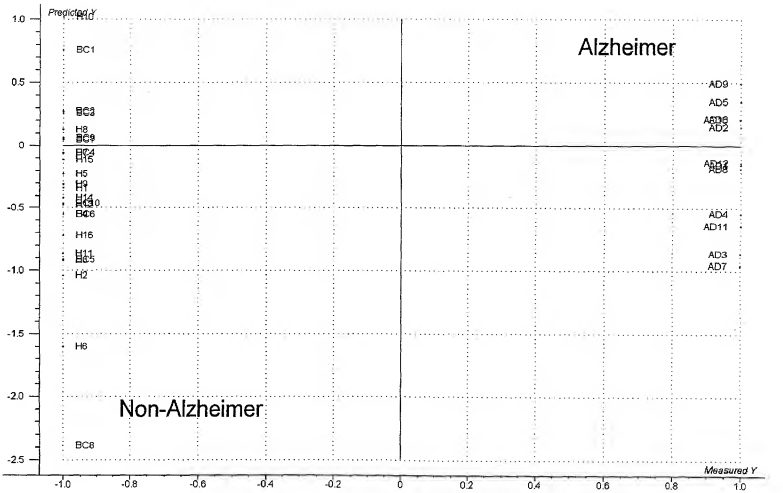
Figure 4

Prediction plot to diagnose Alzheimer's disease samples (set up 1) using 73 probes considered informative for breast cancer

AD = Alzheimer's disease
BC = Breast cancer
H = healthy

Figure 4

Prediction of set up 1 using 73 genes of set up 2



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ANNEX 3

TABLE 4 : Cross-validation and details of the success of the diagnostic test for Alzheimer's disease based on 49 probes considered informative for Alzheimer's disease

A - Validation Result

Total number of samples tested	38
Number of Alzheimer's disease samples tested	12
Number of Alzheimer's disease samples incorrectly diagnosed	9
Number of non-Alzheimer's disease samples tested (healthy and breast cancer)	26
Number of non-Alzheimer's disease samples incorrectly diagnosed	2

B - Success of diagnostic test

Measure of performance	**Description**	**%**
Accuracy	Percentage of the total number of diagnoses that were correct	87
Sensitivity	Percentage of positive cases that were correctly identified	75
Specificity	Percentage of negative cases that were correctly diagnosed	92.3
False positive rate	Percentage of negative cases that were incorrectly classified as positive	7.6
False negative rate	Percentage of positive cases that were incorrectly classified as negative	25
Total error rate	Percentage of the total cases incorrectly diagnosed	13

TABLE 5 : Cross-validation and details of the success of the diagnostic test for breast cancer based on 73 probes considered informative for breast cancer

A - Validation Result

Total number of samples tested	38
Number of breast cancer samples tested	10
Number of breast cancer samples incorrectly diagnosed	2
Number of non-breast cancer samples tested (healthy and Alzheimer's disease)	28
Number of non-breast cancer samples incorrectly diagnosed	0

B - Success of diagnostic test

Measure of performance	**Description**	**%**
Accuracy	Percentage of the total number of diagnoses that were correct	95
Sensitivity	Percentage of positive cases that were correctly identified	80
Specificity	Percentage of negative cases that were correctly diagnosed	100
False positive rate	Percentage of negative cases that were incorrectly classified as positive	0
False negative rate	Percentage of positive cases that were incorrectly classified as negative	20
Total error rate	Percentage of the total cases incorrectly diagnosed	5

TABLE 6 : Cross-validation and details of the success of the diagnostic test for Alzheimer's disease based on 73 probes considered informative for breast cancer

A - Validation Result

Total number of samples tested	38
Number of Alzheimer's disease samples tested	12
Number of Alzheimer's disease samples incorrectly diagnosed	7
Number of non-Alzheimer's disease samples tested (healthy and breast cancer)	26
Number of non-Alzheimer's disease samples incorrectly diagnosed	7

B - Success of diagnostic test

Measure of performance	**Description**	**%**
Accuracy	Percentage of the total number of diagnoses that were correct	63
Sensitivity	Percentage of positive cases that were correctly identified	41.7
Specificity	Percentage of negative cases that were correctly diagnosed	73.1
False positive rate	Percentage of negative cases that were incorrectly classified as positive	27
False negative rate	Percentage of positive cases that were incorrectly classified as negative	58
Total error rate	Percentage of the total cases incorrectly diagnosed	37

TABLE 7 : Cross-validation and details of the success of the diagnostic test for breast cancer based on 49 probes considered informative for Alzheimer's disease

A - Validation Result

Total number of samples tested	38
Number of breast cancer samples tested	10
Number of breast cancer samples incorrectly diagnosed	10
Number of non-breast cancer samples tested (healthy and Alzheimer's disease)	28
Number of non-breast cancer samples incorrectly diagnosed	1

B - Success of diagnostic test

Measure of performance	Description	%
Accuracy	Percentage of the total number of diagnoses that were correct	71
Sensitivity	Percentage of positive cases that were correctly identified	0
Specificity	Percentage of negative cases that were correctly diagnosed	96.4
False positive rate	Percentage of negative cases that were incorrectly classified as positive	4
False negative rate	Percentage of positive cases that were incorrectly classified as negative	100
Total error rate	Percentage of the total cases incorrectly diagnosed	29

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ANNEX 4

TABLE 8 : Sequence and function details of 8 of the 49 Alzheimer's disease informative probes

Clone ID	SEQ ID	Accession number	Regulation Up (+) Down (-)	Putative function
II-24	381	AB043547	+	SMAD4, Growth regulatory factor
III-85	526	AC092671	-	Not known
VII-72	600	AL603650	+	Not known
II-25	382	1915 (Locus link ID)	+	Translation elongation factor 1 alpha 1 (EEF1A1)
II-42	398	8682 (Locus link ID)	-	Cell signalling (phosphoprotein enriched in astrocytes 15)
VII-59	593	6135 (Locus link ID)	+	Ribosomal protein (L11)
VI-04	865	10578 (Locus link ID)	-	Lymphocyte activation gene 519
VI-87	911	6129 (Locus link ID)	+	Ribosomal protein (L7)